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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,366		REGINA RESZKA	2936.169/00	7163

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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	16

DATE MAILED: 07/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/581,366	RESZKA, REGINA	
	Examiner	Art Unit	
	Mary Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24 and 34-46* is/are pending in the application.

4a) Of the above claim(s) *14 and 34-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,23,24 and 37-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election without traverse of Group IV in Paper No. 15, filed 5/7/02, is acknowledged.

Claims 14, 22 and 34-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, inventions encompassed by Group I, PEG-liposomes, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 15, filed 5/7/02.

Specification

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

MPEP 201.11 provides exemplary language for indicating that the Application is a "National Stage of International Application No. PCT/DE98/03763, filed December 14, 1998."

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-13, 15-21, 23-24, and 37-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 is drawn to an agent for effecting gene transfer comprising one or more genetic materials, polymer-modified liposomes, DCES and a contrasting agent. Claim 2 specifies that the genetic materials are DNA, RNA, ribozymes or antisense oligonucleotides. Claim 3 specifies that the genetic materials are therapy genes, anti-angiogenesis genes, apoptosis genes with marker genes. Claims 4-5, 38 and 39 further specify agents for delivery as proteins and specific genes. Claims 6-13, 15-21, 37 and 40 specify further the composition of the liposomes. Claims 23 and 24 are drawn to a method of producing an agent for effecting gene including a therapeutical amount of genetic material. Claims 41-46 are drawn to methods of gene transfer and gene therapy of various disorders including cancers, autoimmune diseases, high blood pressure, etc.

The specification as filed only teaches by way of example making and using particular MLV-PEG liposomes. The specification as filed does not teach by way of example use of the elected (non-PEG) polymer liposomes. The specification thus did not teach by way of example design of the elected polymer liposomes for administration of gene transfer agents, including antisense, ribozymes, genes and proteins for therapeutic purposes.

There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity

but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site

selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful delivery of antisense molecules *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed for delivery of antisense.

As argued in the previous Official Action mailed 05/09/01, there is also a high level of unpredictability for administration of gene therapy genes to whole organisms. Anderson and Reynolds et al. were cited to teach the unpredictability as pertaining to design of vectors for gene delivery. Although the field of gene therapy benefits from optimization of delivery by improvement of liposomal compositions, the active ingredient of the claimed liposomal compositions remains the gene therapeutic agent. As such, with the high level of unpredictability in the art for design of such constructs, one skilled in the art would necessarily practice "trial and error experimentation" to make and use the invention as broadly claimed to design genetic therapeutic constructs for use as compositions having implied therapeutic use. The specific factors considered unpredictable include: (1) formulation, (2) for proteins, size and ability to retain appropriate structure, (3) dosage and routes of administration, (4) entry into the cell, (5) toxicity, (6) vectors and expression of gene therapy genes, and (7) desired treatment effects.

Since the specification as filed does not teach any specific treatment effects using non-PEG polymer liposomes, one of skill in the art at the time the invention was made would have had to practice undue experimentation to make and/use any such therapeutic agent as broadly claimed. Note Fritz et al. who specifically teach the barriers to successful delivery of antisense or plasmids via liposomes. They specifically teach the unpredictability in the art regarding toxicity of the nanoparticle suspensions, the stability of the liposome, the amount of ODN released, etc. On page 280 they taught that "the shape and size of the nanoparticles play an important role for body distribution and irritant tissue reaction." On page 287, they summarize

critical elements in the design of a liposome: charge, surface concentration, density, absorption behavior (the effects of the ODN modifications on these factors), enzymatic degradation, and other environmental conditions such as pH. Since the specification as filed does not teach any specific treatment effects using the claimed polymer-liposome compounds having a specific correlation to treatment in any whole organism, there is no guidance for overcoming the unpredictable factors in the art for making and using any therapeutic agent as claimed. One of skill in the art at the time the invention was made would have had to practice "trial and error experimentation" to make and use any of the therapeutic agents claimed for treatment effects in whole organisms such as human. One of skill in the art would necessarily practice undue experimentation to make and/use any such therapeutic agent as broadly claimed.

Response to Arguments

On pages 10-11 of the response filed 1/3/02, Applicant states that "[t]he novel discovery of applicant's invention is based on the finding of the important role of DCES (preferably starch, but also gelatin or polymer) in carrying the combined liposome-genetic material complex. It has been surprisingly observed that the drug-containing liposomes are 'piggy-backed' on the starch particles. The liposomes, preferably of the PEG form, interact with the starch particles to keep the starch particles attached which the agent moves through the blood stream. Once the agent reaches the site of embolization, the liposome is released from the starch, and the liposomes become trapped in the tumor and being to release the drug over an extended period of time."

From this description, it is clear that the intended use of the liposomes is in a whole organism environment for delivery of a gene therapeutic agent.

Applicant further writes that "[t]he claims are drawn, not to a gene therapy, but to an agent for effecting gene transfer. Applicant need only demonstrate that the skilled person could make such an agent based on a complexing of genetic material and liposomes, with a 'piggy-back' support, such as starch.... It is not necessary to demonstrate that every drug (genetic material) will be effective in treating a particular illness. Success should be measured by the maintaining of the integrity of the agent. The inventiveness lies in the novel combination of the starch and the liposome, which together act to maintain the drug in bound form until a desired time, such as when the tumor is reached."

Claims 41-46 are specifically drawn to methods of treatment however. Further, Applicant's arguments support the intended use of the liposomes as gene therapy delivery agents to whole organisms for a desired action therein. The claims thus are not limited to only a starch and polymer-liposome composition, but specifically comprise gene therapeutic agents having a specific intended function for treatment inside a whole organism. As reiterated above, the claims are not enabled for the claimed compositions for use in a whole organism because of the high level of unpredictability in the art for any administration of a gene therapeutic agent to a whole organism for treatment effects.

5. Non-PEG polymer liposomes were known in the art at the time the invention was made, such as those using poly(acryloylmorpholine) and poly(vinylpyrrolidone). These compounds were taught for instance by U.S. Patents 6,120,751, 6,333,194, 6,028,066, 6,001395 and 5,997898.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Kay Pinkney*, whose telephone number is (703) 305-3553.

M. M. Schmidt
July 29, 2002